



## *IV. Prostate Cancer Research Program*

**Vision:** To conquer prostate cancer.

**Mission:** To promote innovative, multidisciplinary, and regionally focused research directed toward eliminating prostate cancer.

**Congressional Appropriations for Peer Reviewed Research:** \$310M in FY97–01, \$85M in FY02, and \$85M in FY03

**Funding Summary:** 651 awards from the FY97–01 appropriations; 146 awards from the FY02 appropriation; ~210 awards anticipated from the FY03 appropriation

*...shaping the future of health care  
to prevent, control, and cure diseases.*



# Prostate Cancer Research Program

*"I have seen the CDMRP and its Prostate Cancer Research Program up close. The dedication and professionalism of the organization give me confidence that the war against prostate cancer is being won."*

Vin McDonald  
USTOO  
Consumer Advisor

## *The Disease*

Prostate cancer is the most commonly diagnosed cancer in men, accounting for 30 percent of all cancers in men. In 2003, approximately 220,900 men in the United States will be diagnosed with prostate cancer and an estimated 28,900 will die from the disease. Prostate cancer is second only to lung cancer as a leading cause of cancer deaths in men. During the period of 1992 to 1999, the average annual incidence of prostate cancer among African American men was 59 percent higher than among Caucasian men, and the average annual death rate was more than twice that of Caucasian men.<sup>1</sup> Currently, there is no cure for locally advanced or metastatic prostate cancer.

## *Program Background*

The Department of Defense (DOD) Prostate Cancer Research Program (PCRP) was established in fiscal year 1997 (FY97) by Appropriations Conference Committee Report No. 104-863, which provided \$45 million (M) for research in prostate cancer. As a major funder of extramural prostate cancer research, the PCRP has managed \$480M from FY97 to FY03 to fund peer reviewed prostate cancer research. A total of 797 awards has been made through FY02 to promote innovative, multi-institutional, and multidisciplinary research directed toward eliminating prostate cancer. The PCRP has developed a research portfolio that encompasses basic, clinical, and population-based research.

## *The Fiscal Year 2002 Program*

Congress appropriated \$85M in FY02 to continue the peer reviewed DOD PCRP. The FY02 PCRP challenged the scientific community to design innovative prostate cancer research that would foster new directions, address neglected issues, and bring new investigators into the field. The programmatic vision was implemented by requesting proposals in three award categories: (1) research, (2) research resources, and (3) training/recruitment. Table IV-1 provides a summary of the FY02 PCRP award categories and mechanisms in terms of number of proposals received, number of awards, and dollars invested. As illustrated in Figure IV-1, the portfolio of research supported by the FY02 PCRP is diverse.

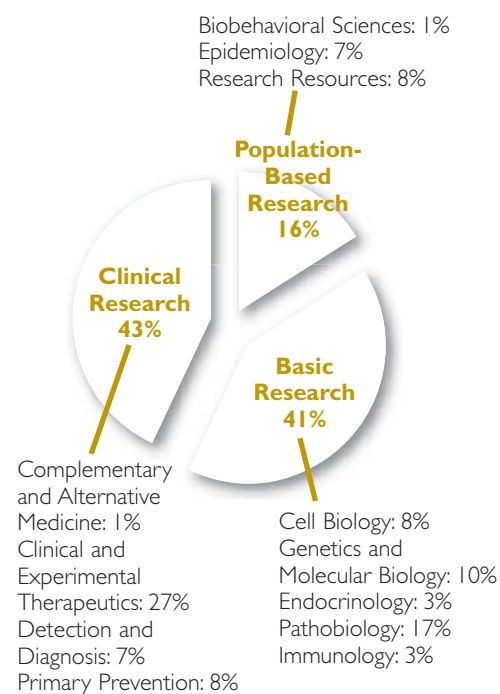
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<sup>1</sup> American Cancer Society - Cancer Facts and Figures 2003.

**Table IV-1. Funding Summary for the FY02 PCRP**

Category and Award Mechanism	Number of Proposals Received	Number of Awards	Investment
<b>Research</b>			
Idea Development	487	83	\$43.8M
New Investigator	141	28	\$9.2M
Health Disparity Research – Prostate Scholar Awards	10	5	\$2.2M
<b>Infrastructure</b>			
Consortium	5	2	\$19.9M
<b>Training/Recruitment</b>			
Health Disparity Training – Prostate Scholar Awards	2	1	\$0.1M
Postdoctoral Traineeships	54	27	\$2.6M
<b>Total</b>	<b>699</b>	<b>146</b>	<b>\$77.8M</b>

For the FY02 PCRP, a total of 699 proposals was received, and 146 were funded. The PCRP continued its emphasis on innovative, high-risk/high-gain research by supporting Idea Development and New Investigator Awards; collectively, 111 awards were made. To address the disparate incidence, morbidity, and mortality among African Americans and other ethnic groups, the PCRP offered Health Disparity Training – Prostate Scholar Awards and Health Disparity Research – Prostate Scholar Awards; collectively, 6 awards were made. A total of 27 Postdoctoral Traineeship Awards were made to stimulate prostate cancer research from talented postdoctoral trainees. A unique feature of the FY02 program was the culmination of the PCRP Consortium Award. This award mechanism supported major, coordinated, goal- and product-driven synergistic research efforts that involve the nation's leading researchers. Two Consortium Awards were made in FY02. (See related box story on page IV-6.)


**Figure IV-1. FY02 PCRP Portfolio by Research Area**



## *The Vision for the Fiscal Year 2003 Program*

Congress appropriated \$85M to continue the PCRP in FY03. As in previous years, the PCRP continued its emphasis on innovation and training. A total of 834 proposals was received, as shown in Table IV-2, and approximately 210 awards are expected.

Nine award mechanisms were offered, six of which were previously established by the PCRP and three were new to the PCRP in FY03, as described below:

- ◆ Physician Research Training Awards are intended to prepare physicians for careers in prostate cancer research through a mentored training experience.
- ◆ Exploration – Resource Development Awards are intended to support product-driven research aimed at developing critical resources (such as animal models, cell lines, and reagent) that are needed to advance the field of prostate cancer.
- ◆ Exploration – Hypothesis Development Awards are intended to support the initial exploration of innovative, untested, potentially groundbreaking concepts (with no preliminary data) in prostate cancer.

Appendix B, Table B-2, summarizes the congressional appropriations and the investment strategy executed by the PCRP for FY02–03.

**Table IV-2. Award Mechanisms Offered and Proposals Received for the FY03 PCRP**

Category and Award Mechanism	Number of Proposals Received
<b>Research</b>	
Exploration – Hypothesis Development	121
Exploration – Resource Development	36
Health Disparity Research – Prostate Scholar Awards	11
Idea Development	392
New Investigator	141
<b>Training/Recruitment</b>	
HBCU Collaborative Partnership	5
Health Disparity Training – Prostate Scholar Awards	4
Physician Research Training Awards	8
Postdoctoral Traineeships	116
<b>Total</b>	<b>834</b>

## *Scientific Outcomes and Advances*

PCRP award outcomes present promise for the future. The following highlighted projects represent a sampling of some of the most exciting advances in prostate cancer research. This broad portfolio of research is laying the foundation for increasing basic knowledge about, treating, improving the lives of individuals affected by, and preventing prostate cancer.

### **Molecular Biology Offers Hope for New Therapies in Prostate Cancer**

**Donald Miller, M.D., Ph.D., P. Bates, Ph.D., and J. Trent, Ph.D.,  
University of Louisville**

The regimens of present day chemotherapy utilize drugs that are toxic to both the tumor and normal tissue. This toxicity can lead to temporarily incapacitating side effects (e.g., nausea, fatigue, and diarrhea), as well as long-term effects. Current treatments for prostate cancer can have dire consequences, such as bladder control problems and sexual dysfunctions. Drs. Miller, Bates, and Trent are exploiting molecular biology techniques to develop new drugs that will specifically target cancer cells. Using G-rich oligonucleotides, which are strings of guanosine (one of the components of DNA), the researchers were able to demonstrate an antiproliferation effect in cancer cell lines from prostate, lung, colon, skin, kidney, and breast. Cell lines derived from highly metastatic prostate cancer were sensitive to the G-rich oligonucleotide analog. To understand these effects and therefore produce better analogs, the mechanism of drug action was investigated. These studies show that the antiproliferative effect observed correlates to binding of the analog to nucleolin, an important molecule in the processing of genes to proteins. In addition, the G-rich oligonucleotide analogs have been found to modulate DNA replication through interaction with a protein called helicase, a known participant in DNA synthesis. Cancer cells are known to have aberrant expression of proteins responsible for DNA and protein synthesis. Taken together, these results offer new hope in the continuing battle against prostate cancer.

Further information about this research can be found in the following publications:

- ◆ Dapic V, Bates PJ, Trent JO, et al. 2002. Antiproliferative activity of G-quartet-forming oligonucleotides with backbone modifications. *Biochemistry* 41:3676–3685.





- ◆ Xu X, Hamhouyia F, Thomas SD, et al. 2001. Inhibition of DNA replication and induction of S phase cell cycle arrest by G-rich oligonucleotides. *J. Biol. Chem.* 276:43221–43230.
- ◆ Bates PJ, Kahlon JB, Thomas SD, et al. 1999. Antiproliferative activity of G-rich oligonucleotides correlates with protein binding. *J. Biol. Chem.* 274:26369–26377.

## **Consortium Awards – Connecting the Nation’s Leading Prostate Cancer Researchers**

Two specific awards funded by the FY02 PCRP are expected to have a major impact in controlling the lethal phenotype of prostate cancer and in determining the basis for the disparate incidence and mortality from prostate cancer in African American men. Consortium Awards were executed in two phases spanning both FY01 and FY02 in which the leading prostate cancer researchers from across the country competed for two \$10M awards. The intent of this award mechanism is to support goal- and product-driven research focused on a critical area of prostate cancer research. One consortium is targeting the lethal phenotypes of prostate cancer; while the other is addressing the disparate mortality rates in African American men. Together, these teams of researchers are racing to end the campaign against prostate cancer.

**Dr. Jonathon Simons of the Winship Cancer Institute at Emory University** is directing a consortium of established senior and leading researchers in prostate cancer from 11 different universities and 8 states to identify novel therapeutic concepts, biomarkers, targets, and agents for treating lethal hormone refractory prostate cancer. Web-enabled videoconferencing and on-line videostreaming data-sharing technologies are being used to connect basic scientists (in tumor biology, bone physiology, molecular genetics, pharmacology, and biostatistics) and physician scientists (urologists, pathologists, radiation oncologists, and medical oncologists) in real time across space. Five multidisciplinary, synergistic teams and two cores have been formed to provide investigators the creative latitude to develop novel therapeutic strategies for attacking the lethal phenotype of prostate cancer. Based on the principles of the Manhattan Project, investigators supported by this consortium are coming together to address a critical and national issue in prostate cancer—human skeletal and visceral metastasis of hormone refractory prostate cancer.

**Dr. James Mohler formerly of the University of North Carolina at Chapel Hill and now of the Roswell Park Cancer Institute** is heading a consortium that includes renowned clinicians and basic scientists from 11 institutions/organizations to uncover the reasons why prostate cancer mortality is higher in African Americans than in Caucasian Americans. This large multidisciplinary study includes 2,000 men from two geographic areas (North Carolina and Louisiana) where prostate cancer mortality rates not only differ between races but also differ between two African American groups. The major end products from this comprehensive and coordinated effort are (1) an invaluable resource of clinical data, serum, adipose tissue, and microarrayed prostate cancer tissue from 1,000 African American men and 1,000 Caucasian American men and (2) characterization of racial differences in patient–health care system interaction and host biology and tumor characteristics. Investigators supported by this consortium are accelerating research progress on the health disparities in prostate cancer through real-time communication and problem solving and by incorporating multiple, parallel projects.

## **Targeting EphA2 in Prostate Cancer Metastases**

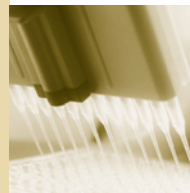
**Elikplimi K. Asem, D.V.M, Ph.D., and Michael S. Kinch, Ph.D.,  
Purdue University, West Lafayette, Indiana**

The Eph family of receptor tyrosine kinases has important roles in the development of complex organs in the fetus but can also have ominous overtones when expressed in cancers. Previous research had found that a member of this family, EphA2, is overexpressed in human prostate cancers as compared with noncancerous prostate tissues. Metastatic prostate cancer cells show even higher EphA2 expression, often 50–500 times higher than prostate cancer cells that do not metastasize. While it is highly expressed on prostate cancer cells, the EphA2 found on metastatic cells cannot hold onto its normal partner protein, ephrin-A, indicating it has in some way changed from its normal shape into a form not recognized by ephrin-A. An Idea Development Award made to Purdue University sought to use the change in the binding capacity of EphA2 to develop antibodies that will only target the cancerous prostate cell and not the normal cell. Several antibodies to the EphA2 found on prostate cancer cells have been made and are being tested in collaboration with MedImmune, a biotechnology company located in Gaithersburg, Maryland. Using a unique three-dimensional assay of tumor cell growth, binding of these antibodies to metastatic cancer cells has been able to reverse the metastatic behavior of the cells in culture and inhibit their growth. The use of these antibodies could provide not only a way to slow tumor growth and metastasis, but also a way to transport therapeutics directly to cancer cells with minimal damage to normal cells. For additional reading about this work, please refer to the following publications:

- ◆ Carles-Kinch K, Kilpatrick KE, Stewart JC, and Kinch MS. 2002. Antibody targeting of the EphA2 tyrosine kinase inhibits malignant cell behavior. *Cancer Res.* 62:2840–2847.
- ◆ Kinch MS and Carles-Kinch K. 2003. Overexpression and functional alterations of the EphA2 tyrosine kinase in cancer. *Clin. Exp. Metastasis* 20:59–68.

*“...the dedication of funded PCRCP scientists and clinicians, the passion of consumer advocates, and the commitment of the CDMRP staff and contractors make this program truly remarkable...”*

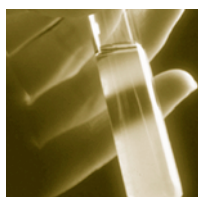
Leo Giambarresi, Ph.D.  
PCRCP Program Manager



## **PMOs and Targeted Therapies for Prostate Cancer**

**Gayathri R. Devi, Ph.D., AVI BioPharma, Incorporated,  
Corvallis, Oregon**

Phosphorodiamidate morpholino oligomers, "PMOs," are a form of manufactured genetic material that bind to RNA, the precursor to protein, and prevent the expression of specific genes. PMOs are not toxic, nor does the body seek to break down the molecules even if given orally. Dr. Gayathri Devi, who was funded at the Oregon Health Sciences Center by the PCRP as a Postdoctoral Trainee in 1998 for studying the insulin-like growth factor (IGF) family and their regulation by proteases in cancer, was also awarded a New Investigator Award to pursue an extension of this work through AVI BioPharma in 1999. Her work focuses on IGF-I



## **Review of the FY99 Prostate Cancer Center Initiation Awards**

The Prostate Cancer Center Initiation Awards were a highlight of the FY99 PCRP. Four awards were made to engage experts from multiple disciplines to establish regional centers for basic and clinical research in prostate cancer. The awards funded innovative research projects as well as expansion of the existing research resources to improve access to cutting-edge facilities and technologies. With the support of the PCRP, the four award recipients – Emory University, University of California at Los Angeles, University of Southern California, and Vanderbilt University – have made important contributions to our understanding of prostate cancer and to the development of new clinical treatments. The results of their research are summarized below.

**Emory University.** Investigators at the Emory Prostate Cancer Research Center seek to improve our fundamental understanding of prostate cancer development and metastasis through multidisciplinary research with laboratory model systems and human tumor tissues. Led by Dr. John Petros, a team of molecular biologists, pathologists, and clinical urologists demonstrated that a protein that produces reactive oxygen species in prostate tumors stimulates the blood vessel formation needed for cancer growth and metastasis. Additionally, the researchers showed that expression of a protein called MUC18 on the surface of prostate tumors increases metastasis. To support these and other projects at this PCRP-supported cancer center, Dr. Petros and colleagues established a shared core facility to provide investigators access to high-quality human prostate tumor specimens, pathology services, and state-of-the-art DNA chip technology. The efforts of the Emory team have resulted not only in the identification of novel targets for prostate cancer treatment, but also in the development of the facilities and resources needed for future research.

**University of California at Los Angeles (UCLA).** Derangements in signal transduction (the transmission of messages from the exterior of the cell to the interior) can cause the loss of normal growth controls and the development of cancer. Dr. Charles Sawyers and his team at UCLA – which includes clinicians, laboratory scientists, and a prostate cancer surgeon – use animal models to study signal transduction in prostate cancer, with an eye toward potential clinical applications. With the assistance of their newly established core animal facility, Dr. Sawyers' group demonstrated that IGF-I signaling in prostate tumors is associated with the development of resistance to

receptor and matrix metalloproteinases (MMPs), in particular MMP-9 as targets for PMO therapy. MMP-9 is a potent IGFBP-3 protease, is elevated after androgen ablation therapy, and is implicated in tumor angiogenesis and metastasis. Following successful studies in cell culture systems, the therapy was tested in a prostate cancer model in mice. The MMP-9 PMO antisense therapy inhibited MMP-9 gene expression, decreased tumor growth, and reduced the formation of new blood vessels in the implanted tumors in mice. More importantly, no toxicity or death was observed in mice treated with the MMP-9 PMO antisense. PMOs appear to be a promising therapy for targeted therapeutic design for prostate and other cancers.

Additional details about this work have been published in the following journal articles:



androgen deprivation therapy, a major clinical problem. Furthermore, they found that an IGF-1 blocking protein kills androgen-independent prostate cancer cells in the laboratory and that an inhibitor of Her-2 signaling blocks androgen-independent prostate tumor growth in mice. This research has led to the development of clinical translational projects with the potential to add to the arsenal of treatment options for advanced, androgen-independent prostate cancer.

**University of Southern California (USC).** Dr. Ronald Ross and his team of molecular biologists, epidemiologists, statisticians, and pathologists at the USC/Norris Prostate Cancer Center seek to understand the genetic factors that contribute to racial and ethnic differences in prostate cancer progression. The ongoing Hawaii–Los Angeles Multiethnic Cohort Study, a prospective study of over 200,000 men in four racial/ethnic groups (African American, Caucasian, Latino, and Japanese American), serves as the core resource for this newly established cancer center. The USC group analyzed mutations in a gene called SRD5A2 in prostate tumor tissue from their multiracial cohort and observed significant variations in biochemical properties and drug responsiveness. Future studies will determine the contributions of these mutations to tumor progression. Dr. Ross' team is currently analyzing the expression of other key proteins in tumor samples, with the aim of identifying novel markers of prostate cancer progression in men of different racial and ethnic backgrounds.

**Vanderbilt University.** The Vanderbilt Prostate Cancer Center, an outgrowth of the prestigious Vanderbilt–Ingram Cancer Center, integrates multidisciplinary basic research with clinical and translational research programs. Dr. Robert Matusik and his team of basic and clinical scientists have developed new mouse models to study the roles of two key growth factors, TGF $\alpha$  and TGF $\beta$ , in prostate cancer. With support from their newly established pathology core facility, Dr. Matusik's group demonstrated that either increased expression of TGF $\alpha$  or blockade of the TGF $\beta$  pathway causes precancerous prostate lesions in mice. The team also showed that TGF $\beta$  signaling may slow the development of androgen independence in prostate tumors. These results support the idea that novel therapeutics targeting TGF $\alpha$  and/or TGF $\beta$  activity may be useful supplements to current prostate cancer treatments.



- ◆ Arora V, Devi GR, and Iversen PL. Neutrally charged PMO: Uptake, Efficacy and Pharmacokinetics. *Current Pharmaceutical Biotechnology* (In press).
- ◆ London CA, Harmanjatinder SS, Arora V, et al. 2003. A novel antisense inhibitor of MMP-9 attenuates angiogenesis, human prostate cell invasion and tumorigenicity. *Cancer Gene Therapy* (In press).
- ◆ Iversen PL, Arora V, Acker AJ, et al. 2003. Efficacy of antisense morpholino oligomer targeted to c-myc in prostate cancer xenograft murine model and a Phase I safety study in humans. *Clin. Cancer Res.* 9:2510–2519.
- ◆ Devi GR. 2002. Antisense therapy for prostate cancer. *Curr. Opinion Mol. Therapy* 4:138–148.
- ◆ Devi GR, Oldenkamp JR, London CA, and Iversen PL. Inhibition of human chorionic beta-subunit modulates the mitogenic effect of c-myc in human prostate cancer cells. *Prostate* 53:200–210.
- ◆ Devi GR, Sprenger C, Graham DL, Plymate SR, and Rosenfeld RG. 2002. IGFBP-3 overexpression induces early apoptosis in malignant prostate cancer cells. *Prostate* 51:141–152.

## **Selenium and the Prostate Cancer Switch**

**Yan Dong, Ph.D., Roswell Park Cancer Institute, Buffalo, New York; and David J. Waters, Ph.D., D.V.M., Purdue University, West Lafayette, Indiana, and the Gerald P. Murphy Cancer Foundation**

The evidence that selenium is a trace element that may help protect men from prostate cancer is mounting. Originally, scientists believed that selenium helped enhance the function of the body's antioxidants and rid the body of potentially damaging agents. However, several studies funded through the PCRP are changing our understanding of how selenium protects men from prostate cancer, and what doses may be best for conferring the protection. Dr. Dong, who received a PCRP Postdoctoral Traineeship Award at Roswell Park Cancer Institute, is finding how selenium may inhibit the growth of prostate cancer cells. She is using technology that allows her to analyze a large part of the human genome on a single silicon chip, finding which genes are turned on or off as a result of selenium. More than 2,500 genes were identified that had changes in expression caused by selenium. Many of the genes are associated with blocking cell cycle progression, inducing apoptosis, inhibiting cell invasion, initiating DNA repair, and stimulating expression of transforming growth

factor- $\beta$  (TGF- $\beta$ ), a gene that is important in controlling proliferation and differentiation through apoptosis.

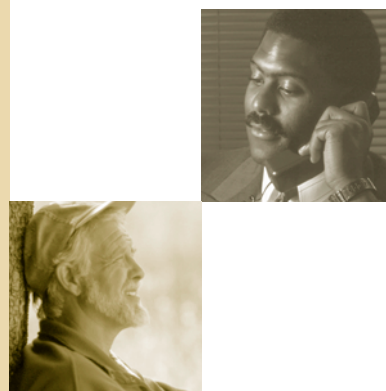
Another PCRP investigator, Dr. Waters from Purdue University and the Gerald P. Murphy Cancer Foundation is using his Idea Development Award to determine what levels of selenium provide the best protection from prostate cancer for men. He is using aged beagles, which other than humans are the only animals to spontaneously and naturally get prostate cancer as they age. The dogs received a diet supplemented with small doses of selenium for a period of 7 months. Following the supplementation period, blood and prostate samples revealed that untreated dogs had high levels of DNA damage in their prostate cells, which could result in prostate cancer. In the selenium-treated dogs, however, the number of cells showing DNA damage was nearly cut in half, and low doses worked as well as high doses in reducing DNA damage. Selenium-supplemented dogs also had pockets of apoptotic cells not seen in the untreated dogs, suggesting that selenium's ability to prevent cancer may come from its ability to switch on apoptosis in genetically damaged cells. Together, these researchers are contributing to our understanding of how selenium confers protection against prostate cancer.

Please refer to the following publications for additional information about this research:

- ◆ Dong Y, Zhang H, Hawthorn L, et al. 2003. Delineation of the molecular basis for selenium-induced growth arrest in human prostate cancer cells by oligonucleotide array. *Cancer Res.* 63:52–59.
- ◆ Waters DJ, Shen S, Cooley DM, et al. 2003. Effects of dietary selenium supplementation on DNA damage and apoptosis in canine prostate. *J. Natl. Cancer Inst.* 95:237–241.

## Summary

While prostate cancer is a complex disease, the PCRP is looking forward to the future when we will understand the mechanisms involved and apply this knowledge toward a cure. Since 1997, the DOD PCRP has been responsible for managing \$480M in congressional appropriations, resulting in 797 awards from FY97 to FY02. The diverse portfolio of funded research is already making important contributions to understanding, preventing, detecting, diagnosing, and treating prostate cancer. Research highlights, award data, and abstracts of funded PCRP proposals can be viewed on the CDMRP website (<http://cdmrp.army.mil>).



## **PCRP Accomplishments – A Snapshot of the First 5 Years**

While the PCRP has supported more than 800 studies of prostate cancer-specific research in the first 5 years, only about 100 projects have been completed. The PCRP anticipates enormous progress in prostate cancer research as the program matures and the investigators funded by the program complete their work. However, examination of the program already shows a return on our investment. Highlighted below is a snapshot of the first 5 years of the program across multiple fronts, from basic science through clinical research.

### **Basic Science Research**

Basic science research provides the first steps toward understanding the fundamental questions of prostate cancer: how it develops, why it grows, and how it becomes aggressive enough to spread to other parts of the body. Understanding these fundamental questions is critical to developing new detection methods, treatments, and possibly a cure for prostate cancer. The PCRP has funded many projects aimed at addressing basic science research, and PCRP-supported investigators have already added critically important information and insights in this arena.

- ◆ *Solving the prostate cancer genetic puzzle.* PCRP-supported investigators have found and are continuing to search for genes that play critical roles in the development of prostate cancer. Three genes discovered through PCRP funding (HPC2/ELAC2, HPCX, and RNASEL) are implicated in hereditary prostate cancer. Another gene, Bin1, was found to be frequently deleted in nonhereditary metastatic prostate cancers indicating that it plays an important role in suppressing the spread of prostate cancer. Research supported by the PCRP on these and other genes is ongoing and is expected to contribute substantially to the development of more precise early-detection methods and more effective therapies. Noted funded researchers contributing to these significant funding include William Isaacs, Johns Hopkins University School of Medicine; George Prendergast, formerly at the Wistar Institute and currently at the Lankenau Institute for Medical Research; and John Witte, Case Western Reserve University.

### **Specialized Cells and Animals**

Without appropriate cell lines and animal models, progress in our understanding of prostate cancer or in the development and testing of new treatment therapies would be severely impaired. The PCRP has made a strong contribution in the development of these essential tools by funding the creation of more than 80 cell lines and 20 animal models.

- ◆ *Cultured cells: The laboratory workhorse.* Laboratory cultured prostate cell lines, which are developed from cells taken directly from prostate glands, are essential for understanding the basic functions of cells. However, normal cells have a limited life span when grown in culture. Through the use of transforming viruses, normal cells can be made to grow indefinitely in a liquid nutrient culture (media) in the laboratory. However, over time, such virus-"immortalized" cells can accumulate abnormal characteristics, losing some of the original characteristics of the normal cell's function. In an innovative approach, Dr. Hahn and his team at Dana-Farber Cancer Institute are using telomerase-immortalized cell lines to study normal prostate cells in culture. Telomerase-immortalized cell lines, unlike some virus-transformed cell lines, can proliferate indefinitely in the laboratory and can function in culture in the same manner as the normal, mortal cells from which they were derived. More importantly, the telomerase-immortalized cells can be used to identify the early genetic changes that lead to prostate cancer development and metastasis in the normal cell. These studies have enormous potential to identify important molecular targets for the development of early prostate cancer treatments.
- ◆ *Developing a better mouse to study prostate cancer.* The mouse is a powerful model system for understanding disease. Sharing nearly all our genes, mice can be engineered to aid in the understanding of the basics of prostate cancer. In Dr. Shen's laboratory, formerly at the University of New Jersey School of Medicine and Dentistry and currently at Rutgers University, mice lacking a specific gene, called Nkx3.1, that is important in

healthy mice for proper prostate development have been created. In humans, expression of the corresponding protein is reduced or missing in up to 80 percent of prostate cancers. Mice that are missing the Nkx3.1 gene develop very early precancerous lesions that normally do not progress to the cancerous stage. The age of the mice at which these lesions appear correlates well with the time frame in humans. This discovery is very important because it links the onset of very early precancerous lesions in the prostate to the loss of a specific gene, a finding that would not have been possible without the use of mice as tools for discovery. Additionally, the fact that these lesions do not progress further suggests that other genetic modifications are required for cancer to develop. PCRP investigators are continuing to look at protein mutations in combination with other known cancer-causing mutations in mice to begin identifying the pathways that lead from precancerous prostate lesions to full-blown disease. These mice, and others developed by PCRP investigators, are available through the National Cancer Institute Mouse Models of Human Cancers Consortium Animal Repository for use by the prostate cancer research community to provide an accurate model of the early stages of prostate cancer development.

### **Clinical Research and Clinical Trials**

Clinical research bridges the gap between the basic research of today and the development and deployment of future therapeutics. The clinical arsenal assembled by the PCRP in the fight against prostate cancer includes chemotherapy, radiation therapy, hypothermia, immunotherapy, and photodynamic therapy.

◆ *Prostate-specific membrane antigen (PSMA): A target for prostate cancer radiotherapy.* Two awards, one to Dr. Warren Heston of the Cleveland Clinic Foundation and another to Drs. Shanker Vallabhajosula and Neil H. Bander of the Weill Medical College of Cornell University, have been at the forefront of the research into a gene encoding a unique protein that is highly expressed in prostate cancers, PSMA. Although PSMA is expressed in all prostate cells, it is highly expressed on prostate cancer cells, and it is the molecule that is detected by the prostate cancer imaging agent ProstaScint® (Cytogen Corporation). Currently, PCRP investigators Drs. Vallabhajosula and Bander are examining whether PSMA can be used as a target for precise delivery of prostate cancer radiotherapy. Monoclonal antibodies that recognize PSMA on prostate cancer cells are coupled with a strong radioactive isotope, yttrium-90. Drs. Vallabhajosula and Bander, who are developing this exciting new therapeutic through Millennium Pharmaceuticals (Cambridge, Massachusetts), have tested the treatment in a Phase I clinical trial, where it was found to be well tolerated and successful in specifically targeting prostate tumors. Phase 2 clinical trials are expected to begin soon. Using this antibody to directly and specifically target prostate cancer is an exciting development and holds real promise as a new therapy for the treatment of this disease.

### **New Detection Methods for Prostate Cancer**

While a cure is being found, new methods are needed that detect prostate cancer in its earliest stages so that the best treatment outcome can be assured. PCRP-funded research is paving the way for better prostate cancer detection.

◆ *Early detection imaging.* Magnetic resonance imaging can provide excellent detail of internal anatomical features, but it cannot reliably be used as a detection method for prostate cancer. Other detection methods that use the cellular or molecular characteristics of prostate cancer can detect the cancer, but cannot provide information on the physical location of the tumor. Drs. Fei and Wilson of Case Western Reserve University plan to combine the detection features of cellular and molecular imaging with high-resolution anatomical magnetic resonance images to aid in identification of prostate cancer for biopsy and treatment. Image-guided systems such as this have great potential to provide physicians with more accurate and minimally invasive biopsy and treatment options for prostate cancer patients.

## *Fiscal Year 2003 Integration Panel Members*

**Frederic Waldman, M.D., Ph.D.  
(Chair)**

University of California at San Francisco

**Ralph deVere White, M.D.  
(Chair Emeritus)**

University of California Davis Medical Center

**Nicholas Vogelzang, M.D.  
(Chair-Elect)**

University of Chicago

**Monica Liebert, Ph.D.  
(Executive Committee  
Member-at-Large)**

American Urological Association

**Gail Prins, Ph.D.  
(Executive Committee  
Member-at-Large)**

University of Illinois at Chicago

**Thomas Carey, Ph.D.**

University of Michigan  
Comprehensive Cancer Center

**Jean deKernion, M.D.**

Los Angeles School of Medicine

**Robert Dreicer, M.D.**

The Cleveland Clinic Foundation

**Philip Kantoff, M.D.**

Dana-Farber Cancer Institute

**Ronald Lieberman, M.D.**

National Cancer Institute

**Mack Roach, III, M.D.**

University of California at San Francisco

**Virgil Simons**

The Prostate Net

**Joseph Smith, Jr., M.D.**

Vanderbilt University School of Medicine

**Howard Soule, Ph.D.**

CaP CURE

**Wendell Van Auken, M.B.A.**

University of California at San Francisco Cancer Center